1. Request for Reconsideration of Finality of Office Action

If the application is not deemed allowable following the present response, Applicant respectfully requests the finality of the 7 July 2010 Office Action be withdrawn. MPEP 706.7(a) states: "Under present practice, second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims, nor based on information submitted in an information disclosure statement filed during the period set forth in 37 C.F.R 1.97(c) with the fee set forth in 37 C.F.R. 1.17(p)." (*emphasis added*)

In accordance with MPEP 706.7(a), Applicant submits:

(1) The previous amendment submitted on 23 April 2010 did not necessitate the new 103 rejection using Ulman as primary reference; and

(2) Ulman was not based on information submitted in an information disclosure statement filed during the period set forth in 37 C.F.R 1.97(c) with the fee set forth in 37 C.F.R. 1.17(p).

Therefore, Applicant should be afforded the opportunity to respond to the new 103 rejection and finality of the 7 July 2010 Office Action should be withdrawn, unless the Application is deemed allowable following this response.

2. Obviousness-type Double Patenting

Claims 18 and 20–25 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly unpatentable over Claims 28–36 and 41 of co-pending application Serial No. 10/523,908. The rejection is provisional because the allegedly conflicting claims of co-pending application Serial No. 10/523,908, *i.e.*, Claims 28-36 and 41, have not yet been patented. Applicant may elect to argue to overcome this ground of rejection or to provide a terminal disclaimer (to the extent necessary) once the present claims have been found to be otherwise allowable and/or once the co-pending application issues as a patent.

3. Rejection under 35 U.S.C. §103(a) over Ulman in view of Schollmayer

Claims 18 and 20–25 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over EP 0663431 A2 ("Ulman"), in view of U.S. 2004/0048779 ("Schollmayer"). The rejection is respectfully traversed because the Office fails to establish a presumption of *prima*

facie case of obviousness.

3.1. Not all claimed features are taught or suggested by the cited documents

Claim 18 is not obvious over the alleged combination of Ulman and Schollmayer (even if motivation existed for such combination, which is not admitted herein), at least because the cited documents fail to teach or suggest all of the claimed features. To establish a *prima facie* case of obviousness, all claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974); *In re Wilson*, 424 F.2d 1382, 165 USPQ 494 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art").

Claim 18 recites:

> A method for preparing a TTS that comprises a rotigotine-containing cement matrix, the method comprising:
>
> > melting and homogenizing components of the cement matrix and rotigotine without solvent in an extruder at a temperature between 70°C and 200°C prior to lamination of the cement matrix.

The alleged combination fails to teach or suggest all claimed features of Claim 18. In particular, Ulman and Schollmayer, singly or in combination, do not teach (1) homogenization with rotigotine and (2) a hot-melt process without using solvent.

(1) **Homogenizing Rotigotine and Cement Matrix**

As stated in the present Office Action, Ulman fails to teach the claimed active agent, rotigotine. Moreover, Ulman is a completely generic document. Ulman teaches no specific agents. Thus, Ulman gives no concrete guidance whatsoever as to which specific bioactive agents are suitable for use in the PSA, let alone a method for incorporating such an agent in the PSA without damaging the agent in the process. Ulman describes that a bioactive agent may be incorporated into the hot-melt pressure sensitive adhesive (p. 5, lines 30-31), but this mere statement does not amount to a teaching of specifically homogenizing rotigotine and a cement matrix. Furthermore, Ulman's exclusive and express focus is on a hot-meltable adhesive for use with hydrophilic drugs, and rotigotine is a lipophilic drug. Although Schollmayer reports the drug rotigotine, Schollmayer does not cure this deficiency because

Schollmayer discusses rotigotine in a solvent-based system and does not teach that rotigotine can be used in a hot-melt process.

(2) **Hot-Melt Rotigotine Process Without Solvent**

Furthermore, Ulman does not teach that rotigotine can be homogenized with a cement matrix in a hot-melt process without solvent. Although, Ulman generally states that their "PSA" does not employ solvents that are found in "traditional" PSAs, it is incredible to contemplate that an ordinary artisan would believe that Ulman stood for the proposition that any drug could be used in Ulman's hot-melt system, and moreover, any drug could be used without solvent, especially since (1) Ulman does not report any actual hot-melt process examples with a drug, and (2) Ulman's express focus is on hydrophilic drugs, not lipophilic drugs.

Schollmayer does not repair the deficiencies of Ulman. Rather, Schollmayer teaches away from the claimed invention because Schollmayer uses a solvent-based system. Schollmayer explicitly recites solvent in each implementation example, for example, methyethyl ketone (paragraph [**0053**]), ethanol (paragraphs [**0057**] and [**0084**]), and heptane (paragraph [**0084**]). These solvents used in the solvent-based method described in Schollmayer would volatilize at the greater than 100°C temperatures needed to produce the hot-melt PSA of Ulman (p. 5, line 13); methylethyl ketone has a boiling point of 79.6°C, ethanol 78°C, and heptane 98.4°C.

Thus, the alleged combination fails to teach all claimed features, particularly melting and homogenizing the components of the cement matrix and rotigotine without solvent, and Claim 18 is not *prima facie* obvious over the alleged combination.

3.2. Disclosures are not combinable because teachings are incompatible

Ulman and Schollmayer teach substantially incompatible methods for preparing a transdermal system, and thus the cited publications are not combinable. Ulman describes a method for preparing a hot-melt adhesive, whereas Schollmayer describes a method for preparing a reservoir system using solvent. As discussed above, Ulman describes a hot-melt process without teaching any specific agent to be included in a PSA system. In fact, Ulman cannot be a primary 103(a) reference against the claimed invention, since it does not recognize technical problems associated with a hot-melt process for rotigotine. Rotigotine is

known to be thermally unstable at temperatures above 25°C and prone to oxidative damage at those temperatures. Based on this, one would expect that hot-melt extrusion of rotigotine to fail, because the active agent would be destroyed in the process of making the transdermal therapeutic system (TTS).

Schollmayer discusses a rotigotine-containing transdermal therapeutic system, but the solution is significantly different from the claimed invention. It should be noted that the methods described in Schollmayer do not involve preparation of an active-substance-containing a cement matrix nor a hot-melt process. Furthermore, Schollmayer uses solvents to make their rotigotine-containing matrix. See, for example, paragraph **[0058]** of Schollmayer.

No motivation exists to modify the hot-melt procedure of Ulman with the disparate, solvent-based method of Schollmayer because Ulman does not recognize problems associated with rotigotine and Schollmayer discusses a different process. These two incongruous methods are incompatible, and one having ordinary skill in the art would not have combined these two publications to make a rotigotine containing TTS using a hot-melt process.

The present Office Action takes pieces from the cited publications and tries to re-construct the claimed invention in a hindsight manner, without taking into account a critical feature of the claimed invention, e.g., the physical/chemical properties of rotigotine. When a compound is known to be thermally unstable and a claimed process involves treating the compound at a high temperature, it would be logical to analyze why it is obvious or non-obvious to make a final product using a high temperature. However, this aspect is not discussed in the present Office Action at all. Instead, the Examiner asserts that the claimed method is mere "optimization" of existing patch technology. *See* current Office Action, p. 5. Applicant respectfully disagrees with the Examiner's view. The present invention cannot constitute "optimization", because there was no known method to be optimized at the time of the present invention. Optimization refers to an act, process, or methodology of making something as fully perfect, functional, or effective as possible, for example, finding a best working temperature range of a known process. Ulman cannot be a basis for optimization because one does not optimize a system by adding an active agent to it. Schollmayer cannot be optimized because it is a totally different method, *i.e.,* a solvent-based method. The system

and the active agent are separate and distinct, and are not "optimized" by each others presence. It is respectfully submitted that the Examiner mischaracterizes the teaching of Schollmayer by not considering its full context. It is irrelevant whether Schollmayer teaches the desirability to incorporate rotigotine in any silicone-based pressure sensitive adhesive system. The relevant teaching is whether such incorporation could be performed at a hot-melt temperature (*i.e.* a hot-melt process), to which Schollmayer is completely silent.

As shown above, the methods of Ulman and Schollmayer are substantially different and even incompatible. Therefore, it should not be allowed to take pieces from those publications and construct a method with the pieces in a hindsight manner unless the Office provides reasons why such piecemeal items can be combined despite the incompatibility.

3.3. No rationale to modify the cited art to include the missing subject matter

Where the combined references are missing claimed features, a case of obviousness requires an apparent reason, based either on the references themselves or on the general knowledge in the art, by which a skilled artisan would modify the references to include the missing subject matter. See *KSR Int'l Co. v. Teleflex Inc.,* 127 S.Ct. 1727, 82 USPQ2d 1385 (2007) (obviousness includes determining whether there was an apparent reason to combine known elements in the fashion claimed).

As discussed in Section 3.2, Ulman does not provide any guidance to a person having ordinary skill to solve problems associated with a hot-melt process for oxidation-sensitive drugs, and thus, cannot be the primary document in this §103(a) rejection. In other words, Ulman is not modifiable to become a hot-melt process for preparing a rotigotine-containing TTS without solvent. Furthermore, the alleged combination, even if combinable, is devoid of any suggestion or appreciation of (1) melting and homogenizing rotigotine and cement matrix and (2) without solvent.

The present Office Action fails to provide any basis for an ordinary artisan to forgo such use of solvent with rotigotine or include the present melting and homogenizing processes, as required by *In re Kahn*, 441 F3d 977, 78 USPQ2d 1329 (Fed. Cir. 2006) ("rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning to support the legal conclusion of obviousness"). In contradistinction, the present specification illustrates several advantages

and benefits over solvent-based systems (see specification, paragraph **[0008]**). Absent the articulated reasoning required by *In re Kahn* and by *KSR*, the combination of Ulman and Schollmayer cannot support a presumption of *prima facie* obviousness. No suggestion is made in either Ulman or Schollmayer that rotigotine would be stable in the claimed TTS production method.

3.4. Predictability of outcome required for *prima facie* obviousness is lacking

If rotigotine decomposes at high temperatures, than how could one know it would work in a hot-melt TTS? Rotigotine is known to be very susceptible to oxidation; that is, rotigotine tends to decompose at a higher temperature in oxidative fashion. Thus, not only would one not have been able to predict that rotigotine could be used in a hot-melt process, i.e. be exposed to temperatures up to 160°C, one would have actually expected failure. Further, it could not have been predicted that rotigotine would be released from matrices prepared in this way in a continuous fashion and at a therapeutically desirable rate (specification, paragraph **[0026]**). However, it was surprisingly discovered by the present inventors that, despite rotigotine's known susceptiblity to oxidation, rotigotine actually is compatible with hot-melt technique. Rotigotine remains stable on melting and is present in the resulting matrix at a purity level that is routinely better than 98% and generally over 99%, as measured at 220 nm and 272 nm by HPLC (specification, paragraph **[0027]** and Tables 2, 3 and 4). It should be understood that high drug-loaded solid dispersion with high drug dissolution enhancement is not an easy task since the drug presented in such a system has high crystallinity. Despite these difficulties, Applicant has provided a method for preparing a hot-melt TTS that comprises a rotigotine-containing cement matrix with a high concentration of rotigotine and with high drug dissolution enhancement. Also, the claimed method enables a cement matrix to include higher rotigotine concentrations than other layers prepared by solvent-based processes. Furthermore, the present invention provides improved safety and processing times (specification, paragraph **[0030]**).

None of these advantageous outcomes were predictable from each of Ulman and Schollmayer or any combination thereof. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art (MPEP 2143.01.III, citing *KSR*, *supra*). For

at least this reason, the present claims are not *prima facie* obvious over the cited art.

3.5. Conclusion

In sum, the Office has not established a presumption of *prima facie* obviousness of Claim 18 directed to a method for preparing a rotigotine-containing TTS because (1) the alleged combination does not teach all claimed features; (2) the cited publications are not combinable because teachings are incompatible; (3) there is no rationale to modify the cited art to include the missing subject matter; and (4) predictability of outcome required for *prima facie* obviousness is lacking.

Claims 20-25 depend directly or indirectly from Claim 18 and are non-obvious at least for the same reasons as Claim 18 is non-obvious. Withdrawal of the present 35 U.S.C. §103(a) rejection over Ulman in view of Schollmayer is respectfully requested.

4. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated, or rendered moot herein. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance.

If personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number below.

Respectfully submitted,

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